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Gene Section

Review

DNMT3B (DNA (cytosine-5-)-methyltransferase 3 beta)

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Identity

Other names: ICF, ICF1, M.HsaIIIB
HGNC (Hugo): DNMT3B
Location: 20q11.21
Note
DNA (cytosine-5)-methyltransferase 3B (DNMT3B) is one of the three known DNA methyltransferases with catalytic activity.
This enzyme is responsible for the de novo methylation of DNA, particularly during embryogenesis (Okano et al., 1999). In fact, DNMT3B adds methyl groups to CpG dinucleotides of unmethylated DNA for establishment of new methylation pattern in genomic DNA. DNMT3B level is profoundly increased in various tumor cell lines and in numerous types of human cancers, indicating that it plays an important role in tumorigenesis (Turek-Plewa and Jagodzinski, 2005).

DNA/RNA

Description

DNMT3B gene is located on the long arm of chromosome 20 at position 11.2 and is composed of 23 exons and 22 introns. This gene encodes for a protein of 853 aa. DNMT3B gene is abundantly expressed in embryonic stem cells, but its expression is decreased upon their differentiation and remains low in adult somatic tissues.

Transcription

Primary transcript of DNMT3B gene can be spliced five different mRNA isoforms that are DNMT3B1, DNMT3B2, DNMT3B3, DNMT3B4 and DNMT3B5.

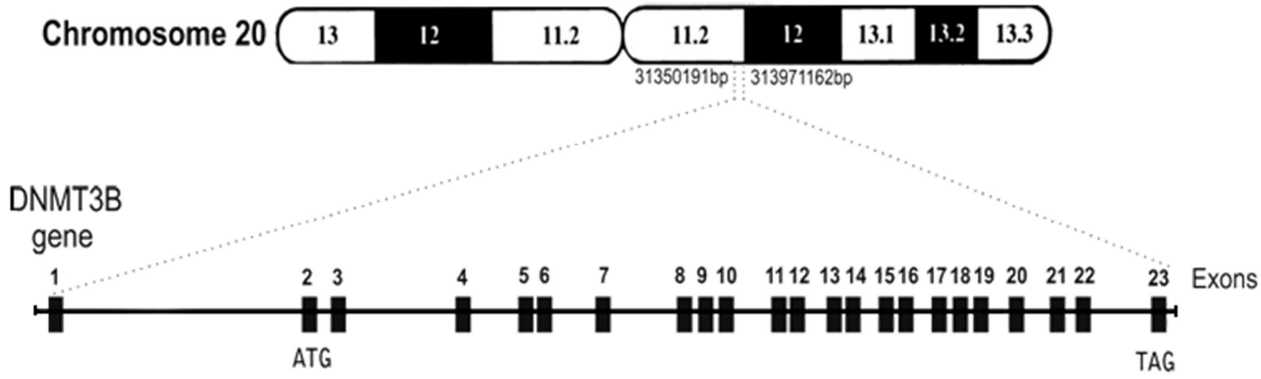

Figure 1. DNMT3B gene is located on the long arm of chromosome 20 at position 11.2 from the base pair 31350190 to base pair 31397161. It is composed of 23 exons and 22 introns.

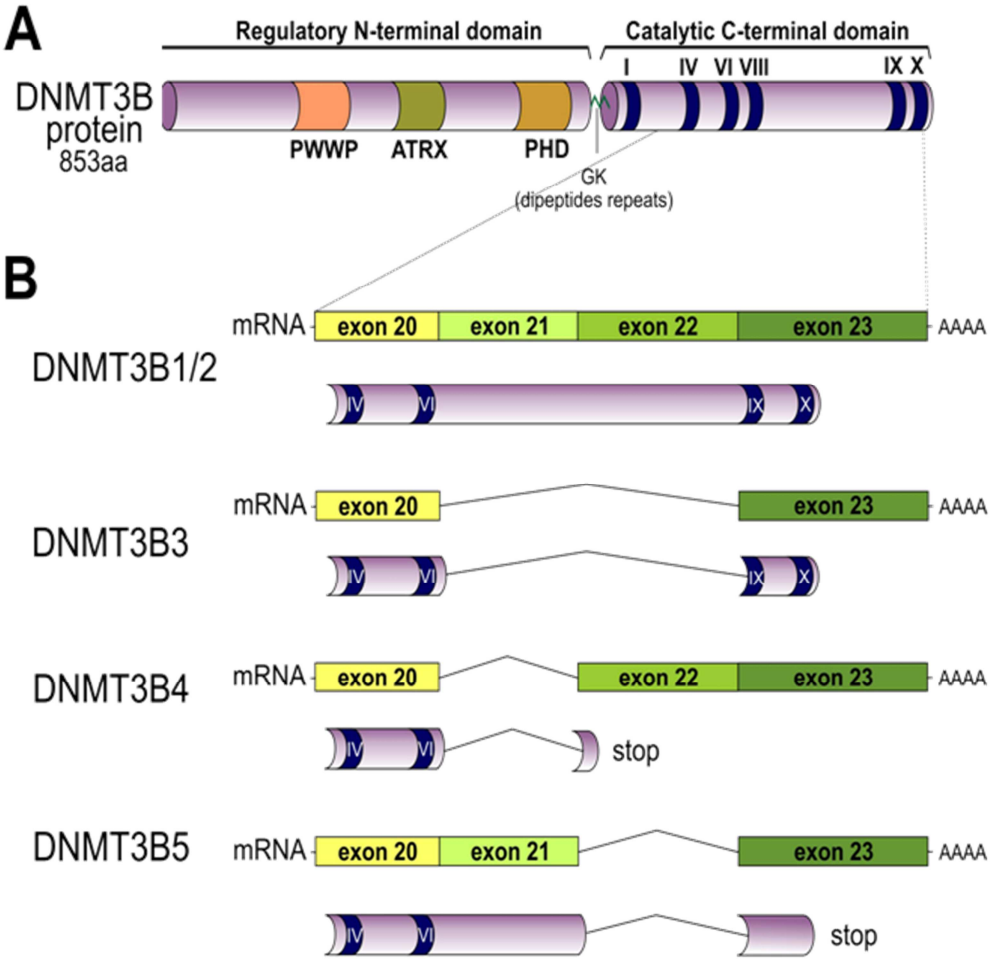

Figure 2. A: The general structure of DNMT3B protein. The N-terminal domain contains a proliferating cell nuclear antigen-binding domain, a nuclear localization signal, a tetrapeptide PWWP, essential for DNMT binding to chromatin, an ATRX cysteine-rich zinc finger DNA-binding motif and a polybromo homology domain (PHD) targeting DNMT3B to the replication foci. The C-terminal catalytic domain of DNMT3B is characterized by the presence of 6 conserved amino acid motifs, namely I, IV, VI, VIII, IX and X. Motifs I and X form S-adenosylomethionine binding site, motif IV binds cytosine at the active site, motif VI possesses glutamyl residue donating protons, and motif IX maintains the structure of the target recognition domain (TRD) usually located between motifs VIII and IX, that make base-specific contacts in the major groove of DNA (Turek-Plewa and Jagodzinski, 2005). **B:** The results from alternative splicing of exons 10, 21 and/or 22, have reported several different transcripts of DNMT3B. These isoforms are: DNMT3B1, DNMT3B2, DNMT3B3, DNMT3B4 and DNMT3B5. DNMT3B1 and DNMT3B2, contain all the highly conserved motifs I, IV, VI, IX and X, are enzymatically active in DNA methyltransferase essays. DNMT3B3, which lacks parts of motif IX, appears to be inactive enzyme. DNMT3B4 and DNMT3B5, encode truncated proteins that lack motifs IX and X, are presumably inactive as well. The lack motifs in DNMT3B3, DNMT3B4 and DNMT3B5 are a consequence of lack 21-22, 21 or 22 exons, respectively (Xie et al., 1999; Okano et al., 1999).

Protein

Note

DNMT3B protein is structured with N-terminal regulatory and C-terminal catalytic domains that are linked by repeated GK dipeptides (Glycine-Lysine-repeats). The N-terminal domain possesses nuclear localization signal sequence (NLS) responsible for nucleus DNMT3B localization. The N-terminal domain plays a regulatory role, and contains a proliferating cell nuclear antigen-binding domain. This N-domain also contains a cysteine rich zinc finger DNA binding motif (ATRX), a polybromo homology domain (PHD) targeting DNMT3B to the replication foci and a PWWP tetrapeptide chromatin-binding domain (Margot et al., 2000). The two halves are packed against each other to form a single structural module that exhibits a prominent positive electrostatic potential. The PWWP domain of DNMT3B alone binds DNA in vitro, probably through its basic surface, and DNMT3B binds DNA stronger than a mutant without the domain. In addition, the PWWP domain seems to target the de novo methyltransferases to chromatin. The C-terminal domain contains six conservative motifs I, IV, VI, VIII, IX and X. Motif I and X are involved in the formation of the S-adenosylomethionine binding site. Motif IV binds the substrate cytosine at the active site. Motif VI contains the glutamyl residue serving as a proton

donor. Motif IX maintains the structure of the target recognition domain (TRD). Motif VIII's function is unclear (Xie et al., 1999).
The intracellular distribution of DNMT3B enzyme is rather dynamic throughout the cell cycle, indeed this enzyme is diffusely distributed throughout the nucleoplasm during most of G1, associates with subnuclear sites of DNA replication during S-phase (Leonhardt et al.,1992), and binds to chromatin, with preference to pericentric heterochromatin, during G2 and M-phases (Easwaran et al., 2005).

Description

853 amino acids; 95751 Da.

Localisation

Nucleus.

Function

DNMT3B is expressed at very low levels in most tissues except the testis, thyroid and bone marrow (Xie et al., 1999). DNMT3B level is profoundly increased in various tumor cell lines, indicating that it plays an important role in tumorigenesis (Robertson et al., 1999; Hermann et al., 2004). DNA methylation is a covalent chemical modification, resulting in the addition of a methyl (CH3) group at the carbon 5 position of the cytosine ring. DNMT3B uses S-adenosyl-L-methionine (AdoMet) as the source of the methyl group being transferred to the DNA bases. The methyl group of S-adenosylomethionine is bound to a sulphonium atom, which thermodynamically destabilizes the molecule and makes the relatively inert methylthiol of the methionine moiety very reactive towards nucleophilic attack by nitrogen, oxygen and sulphur atoms or activated C atoms (carbanions).
DNMT3B may also interact with DNMT1 and activate HDAC1, which deacetylates histones and represses gene transcription.
This indicates that DNMT3B may be involved in chromatin remodeling associated with the modulation of gene transcription. DNMT3B can also effectively methylate C to m^5C post-replicatively in unmethylated DNA. During or after replication, DNA regions may bind sequence-specific proteins which block the attachment of the methyl group to CpG dinucleotide and the formation of methylation patterns unique for each tissue.
The existence of DNMT3B isoforms suggests that other factors can be involved in the binding of DNMT3B to a particular DNA region. Consequences of alternative splicing on DNMT3B's ability to interact with DNMT3L. DNMT3L stimulates the catalytic activity of DNMT3A and DNMT3B methyltransferases (Suetake et al., 2004). DNMT3L binds to the carboxyl-terminal part of DNMT3B and increases the level of activity of this enzyme (Suetake et al., 2004).

Homology

DNMT3B exhibit a high degree of primary structure homology with DNMT3A. Structurally, DNMT3B and DNMT3A have a similar organization, with conserved domains: the long N-terminal region contains a PWWP domain and a cysteine-rich PHD zinc finger domain and the C-terminal catalytic domain. The same NLS and ATRX sequences were also founded in the DNMT3B and DNMT3A enzymes.

Mutations

Note

ICF syndrome (standing for Immunodeficiency, Centromere instability and Facial anomalies syndrome) is a rare autosomal recessive immune disorder caused by mutations of the gene DNMT3B. Therefore, the DNMT3B mutations, like A766P and R840Q, observed in patients are the likely underlying cause of their ICF phenotypes (Xie et al., 2006).
This hereditary syndrome is characterized by centromeric instability of chromosomes 1, 9, and 16 is associated with abnormal hypomethylation of CpG sites in their pericentromeric satellite regions (Hansen et al., 1999). At the molecular level, in patient DNA, sequences such as the pericentromeric classic satellite repeats of pericentromeric regions are hypomethylated, which attributes to reduced enzymatic activity of the mutant proteins (Jeanpierre et al., 1993; Gowher and Jeltsch, 2002).
Several polymorphisms were detected at the promoter region of DNMT3B gene and may influence its activity in DNA methylation and increase the susceptibility to several cancers. DNMT3B promoter polymorphisms influence on promoter hypermethylation of genes in other interacting pathways, such as cell cycle, apoptosis, or other DNA repair pathways and may increase level of DNA damage which contributes to an increased risk for cancers. For example, C>T (rs406193), -283T>C (rs121909506), -579G>T (rs2424909), -579G>T (rs2235758) and G39179T DNMT3B polymorphisms influence DNMT3B expression, thus contributing to the genetic susceptibility to different cancers (Lee et al., 2005; Fan et al., 2008; Montgomery et al., 2004; de Vogel et al., 2009; Daraei et al., 2011).
The common DNMT3B -149C>T (rs2424913) polymorphism was found to significantly increase DNTM3B promoter activity. This up-regulates the expression of the gene and may in turn lead to aberrant methylation of CpG islands in some tumor suppressor genes (Montgomery et al., 2004). It was associated with an increased risk for lung cancer (Shen et al., 2002), prostate cancer (Singal et al., 2005), and colorectal polyps, including colorectal adenomas (Jung et al., 2008), or with prognosis of head and neck cancer (Wang et al., 2004).

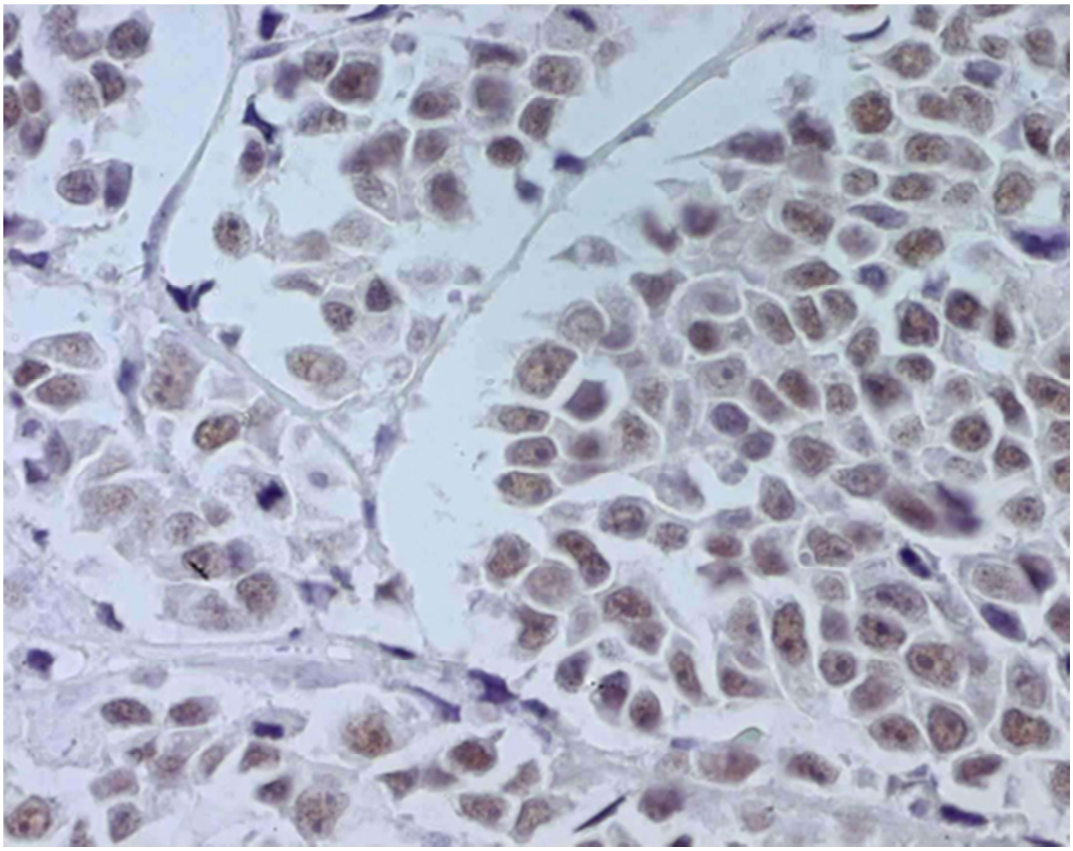

Figure 3. DNMT3B overexpression in breast cancer cells as detected by immunocytochemistry (original magnification x400).

Implicated in

Lung cancer

Note

DNMT3B may play an oncogenic role during tumorigenesis, and its genetic variants have been consistently associated with risk of several cancers. Overexpression of DNMT3B may result in promoter hypermethylation of multiple tumor suppressor genes and ultimately lead to lung tumorigenesis and poor prognosis especially among smoking patients (Lin et al., 2007; Palakurthy et al., 2009).

Polymorphisms and haplotypes of the DNMT3B gene may influence DNMT3B activity on DNA methylation, thereby modulating the susceptibility to lung cancer. The -283T>C and -579G>T polymorphisms in the DNMT3B promoter, and their haplotypes were significantly associated with the risk of adenocarcinoma of the lung (Lee et al., 2005). These mutations up-regulate DNMT3B expression, resulting in a predisposition towards aberrant de novo methylation of CpG islands in tumor suppressor genes and DNA repair genes (Lee et al., 2005; Shen et al., 2002).

Breast cancer

Note

DNMT3B expression levels are significantly higher in breast cancers than in normal breast tissues, suggesting a role of this enzyme in breast tumorigenesis (Fig. 3) (Girault et al., 2003; Butcher and Rodenhiser, 2007; Ben Gacem et al., 2012). DNMT3B overexpression is correlated to the epigenetic inactivation of several tumor suppressor genes and to the aggressive phenotype in breast tumors (Roll et al., 2008; Ben Gacem et al., 2012). Some polymorphisms are associated to the development of breast tumors. DNMT3B C46359T polymorphism has been correlated to women with early-onset breast cancer, bilateral breast cancer and with a family history of the disease (Montgomery et al., 2004; Wang et al., 2004).

Leukemia and lymphomas

Note

DNMT3B is substantially overexpressed in leukemia cells than in normal bone marrow cells (Mizuno et al., 2001). DNMT3B overexpression was correlated to hypermethylation of several tumor related genes in diffuse large B-cell lymphomas and in B-cell chronic lymphocytic leukemia (Amara et al., 2010; Kn et al., 2004). In B-cell chronic lymphocytic leukemia, DNMT3B overexpression was identified as an independent prognostic factor for predicting shortened survival of patients (Amara et al., 2010).

Hepatocellular carcinoma

Note

DNA hypomethylation on pericentromeric satellite regions is one of the earliest events during hepatocarcinogenesis. Overexpression of DNMT3B4 isoform and elevation of the ratio of DNMT3B4 mRNA to DNMT3B3 mRNA were both significantly correlated with the degree of DNA hypomethylation on pericentromeric satellite regions in hepatocellular carcinoma (Saito et al., 2002). DNMT3B4 overexpression induces DNA demethylation on pericentromeric satellite regions even in precancerous stages and may play critical roles in the development of hepatocellular carcinoma through chromosomal instability and aberrant expression of cancer-related genes (Saito et al., 2002).

Colorectal cancer

Note

The levels of DNMTs mRNA/protein in colorectal carcinomas are significantly higher than in noncancerous colorectal tissues and the highest expression range was observed with DNMT3B (Eads et al., 1999; Linhart et al., 2007; Nosho et al., 2009; Huidobro et al., 2012). The CpG island methylator phenotype (CIMP) in colorectal cancer is characterized by a widespread CpG island methylation. DNMT3B contributes to CpG island methylation, which may eventually lead to the development of CIMP-high colorectal cancer (Nosho et al., 2009; Schmidt et al., 2007).

In hereditary nonpolyposis colorectal cancer, the DNMT3B gene contains a C-to-T single nucleotide polymorphism -149 bp from the transcriptional start site that may result in increased promoter activity of the gene (Shen et al., 2002). The DNA mismatch repair mutation carriers who also carried at least one T allele for the DNMT3B promoter region C-to-T polymorphism had a 2-fold higher risk for colorectal cancer by year than those who were homozygous for the wild-type DNMT3B allele (Jones et al., 2006).

Facial anomalies syndrome (ICF)

Note

Facial anomalies syndrome (ICF) is an autosomal recessive disease. DNMT3B gene is often the site of ICF mutations (Ehrlich et al., 2006). ICF syndrome presents with variable combined immunodeficiency, mild facial anomalies and extravagant cytogenetic abnormalities with largely affect the pericentric regions of chromosomes 1, 9 and 16. These pericentric regions contain a type of satellite DNA termed classical satellite, or satellites 2 and 3. It is normally heavily methylated, but is nearly completely unmethylated in DNA of ICF patients. In addition to classical satellite, demethylation of DNA in ICF patients is also seen at CpG islands on the inactivate X chromosome in females (Ehrlich et al., 2008).

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